NEUROPROTECTIVE STRATEGY FOR ALZHEIMER'S DISEASE: INTRANASAL ADMINISTRATION OF NEUROPEPTIDES, I. Gozes, A. Davidson, A. Bardea, M. Bechar, E. Giladi, S. Rubinraut*, M. Fridkin* and D. E. Brenneman**, Clinical Biochem., Sackler Med. School, Tel Aviv University, Isreal; *Organic Chemistry, Weizmann Inst., Rehovot, Isreal and **NICHD, NIH, Bethesda, MD 20892, USA

Vasoactive intestinal peptide (VIP) has been shown to be neuroprotective and play a significant role in the acquisition of learning and memory. A 100-fold more potent lipophilic analogue to VIP (J. Pharmacol. Exp. Therap. 273:161, 1995) has now been synthesized (stearyl-N1e^{17}-VIP), that exhibited neuroprotection in model systems related to Alzheimer's disease. Neuroprotection was observed at subpicomolar concentrations against the beta amyloid neurotoxicity *in vitro*. Intranasal delivery prevented impairments in spatial learning and memory associated with cholinergic blockade [achieved in rats by blockade with ethyl choline aziridium (AF64A)](Proc. Natl. Acad. Sci. USA 93:427, 1996). To further evaluate the breadth of neuroprotection in Alzheimer's-related models, mice deficient in apolipoprotein E (ApoE, Cell 71, 343, 1992) were tested as well. ApoE has been associated with neurotrophic function following injury as well as with the pathology of Alzheimer's disease. Our results indicated that ApoE-deficient mice exhibited retardation in the acquisition of developmental milestones. Furthermore, brains from these mice displayed a marked reduction in the mRNA encoding for VIP. Daily treatment with stearyl-N1e^{17}-VIP resulted in a significant improvement in the acquisition of the behavioral milestones, even earlier than observed in control animals. The neuroprotective activity of VIP is mediated via glial cells and secretion of growth factors from glial cell that in turn control neuronal survival (J. Cell Biol. 104:1603, 1987). A new neuroprotective protein (14,000 Daltons, pI: 8.3 $\pm$ 0.25) secreted by astroglial cells in the presence of VIP was recently isolated and named activity-dependent neurotrophic factor (ADNF), as it protected neurons from death associated with electrical blockade. This protein exhibited structural similarity to hsp60 and neuroprotective activity in unprecedented femtomolar concentrations (J. Clin. Invest. In press). A 14-amino acids peptide derived from this novel growth factor exhibited neuroprotection in the above-mentioned disease models. Our studies suggest a new therapeutic strategy for Alzheimer's disease with lipophilic VIP-related molecules. Furthermore, these studies identify a potent neuroprotective hsp-like glial protein and peptide that may mediate VIP functions and provide a basis for developing novel preventative treatments for Alzheimer's and other neurodegenerative diseases.

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